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BISPHOSPHONATE SAFETY

Bisphosphonates (bps) are well tolerated by the majority of patients, but there is accumulating evidence associating bp therapy with the risk of serious adverse effects (SAE) such as osteonecrosis of the jaw, atypical fractures, atrial fibrillation and esophageal cancer. SAE events with bp doses used for osteoporosis are either rare (occuring in < 1 in 1000 patients), uncertain, or both. For patients at high risk of fracture, the benefits of bps will outweigh these potential harms. However, for patients at low-moderate risk of fracture, concerns about bp safety, especially long term, may outweigh benefits. Table 1 summarizes the risks versus benefits of bisphosphonates when used in the treatment of osteoporosis.

Table 1: Benefits vs. Risk of Harm Due to Serious Adverse Effects of Bisphosphonates

Effect	Estimated three year benefit / harm	Source / Comments
Hip fractures	NNT = 91	RxFiles Treatment Comparison Chart Alendronate, risedronate NNT for 2° prevention only; no significance for 1° prevention
Vertebral fractures	NNT = 13-27	RxFiles Treatment Comparison Chart Risedronate not significant for 1° prevention
Atrial fibrillation (serious)	NNH = 118 (zoledronic acid NNH = 313 (alendronate)	Ref. # 28 zoledronic acid - Randomized Controlled Trial Ref. # 29 alendronate - Case Control Study Other studies report no increased risk of AF
Atypical fractures	?	Too little data; concern with long-term therapy
Esophageal cancer	NNH = 1000 *for 5 years*	Ref. # 7 – case control analysis. Increased risk did not appear until after 4 – 5 year of bp therapy.
Osteonecrosis of the jaw	?	Too little data for bp therapy in OP but concern with high dose/IV bp in cancer patients

Gastrointestinal (GI) EFFECTS

- Most frequent reason cited for discontinuation of therapy with bps.[1] For example, in a telephone survey of women taking anti-osteoporosis medications, 9 % of women taking alendronate reported stopping the drug because of GI side effects (NNH = 11).[2]
- Non-nitrogen containing bps (etidronate) – fewer GI effects, mainly diarrhea.[1]
- For nitrogen-containing bps (alendronate, risedronate) – perception that GI symptoms such as nausea, dyspepsia, abdominal pain, gastritis are common but multiple studies report no significant difference in incidence of symptoms among risedronate, alendronate and placebo.[3]
- Esophageal cancer
    - 23 cases reported in US[3]; 31 in Europe /Japan[4]; reduced incidence rate in bp users versus non-bp users observed in recent Danish

national data. [4]
    - Two recently published case control studies, both utilizing data from the UK's General Practice Research Database provide conflicting results on the association between bps and esophageal cancer possibly due to differences in length of follow-up [5]: 4.5 years – no association [6]; 7.5 years – absolute increase in risk 1 in 1000 after 5 years of use [7].
- Mechanisms proposed for esophageal erosion [2]
    - Direct contact between drug and mucosa causing damage to hydrophobic barrier on mucosal surface.
    - Inhibition of the mevalonate pathway which could hinder mucosal healing.

Management:
- Not necessary to avoid bps because of history of upper GI complaints [except for esophageal abnormalities such as stricture or achalasia (motility disorder) [8], Barrett's esophagus - FDA contraindication [3]].
- If GI symptoms occur, it may be appropriate to rechallenge with the same or a different bp. [3,9]
- Emphasize the importance of following recommended administration procedure for oral bps to reduce the risk of esophageal cancer. These recommendations include taking the bp with a full glass (200 – 250 ml) of water while standing or sitting at least 30 minutes before the first meal of day and not lying down for at least 30 minutes and until after the first meal of the day. [5]
- Use of proton pump inhibitors or other acid suppressants may exacerbate loss of bone density & possibly increase fracture risk[10] so may not be an appropriate long-term solution for bp-induced GI symptoms. [2]
- If patient is unable to tolerate oral bps, consider
    - weekly or monthly dosing regimens. Less frequent administration may also result in better adherence as administration precautions do not have as big an impact on day to day life.
    - parenteral bps (IV zoledronic acid).

Musculoskeletal Effects
- **Acute Phase Reaction**
    - Common with IV bps: occur in 1 in 3 patients after 1st infusion, 1 in 15 after 2nd; 1 in 35 after 3rd [9]; much less frequent with oral bps (< 1 in 100 on initiation of therapy) [3].
    - Incidence is higher with weekly or monthly oral doses compared to daily bps[12]; for example 0.6% with intermittent oral risedronate vs. 0% with daily oral risedronate over 1 year [13].
    - Idiosyncratic self-limiting reaction. Symptoms resolve in a few hours to a few days.[2]

    Management:
    - Antipyretics/analgesics.
    - Consider starting patients on daily oral bps for a few weeks before switching to weekly or monthly.

- **Severe musculoskeletal pain**
    - FDA Alert issued in 2008 for severe musculoskeletal pain occurring from 2 weeks to several years after initiation of bp therapy. [14]
    - Characterised by intense generalized muscle and/or bone pain with fatigue; isolated bone or joint pain is rare. [2]
    - Incidence unknown – may be underreported, risks factors unknown.[3]

Management:

- Pause and rechallenge in mild cases: discontinue in more severe cases. [2]
- Symptoms improve after bp withdrawal in some cases but resolve slowly or incompletely in others. [9]
- Counsel patients to report unexplained musculoskeletal pain promptly. [9]

- **Osteonecrosis of the jaw (ONJ)**
  - Area of exposed bone in maxillofacial area which does not heal.
  - Risk increases with higher dose, longer duration of bp therapy; more common when higher dose of bps are used IV for treatment of cancer. [2]
  - For lower doses of bps used for osteoporosis, incidence appears to be rare: estimates vary from 1 – 10 per 100,000 patient-years [15] to 28 per 100,000 patient years (16) but it is acknowledged that ONJ is likely underreported [2].
  - Mechanism is not understood – jaw site of high bone turnover – bp could accumulate there → oversuppression of bone remodelling → microcracks, osteocyte death and matrix necrosis. [2]
  - Risk factors: poor dental hygiene, dental surgery, periodontitis, cancer chemotherapy and corticosteroid therapy. [2,3]

Management:

- Counsel on good dental hygiene, regular dentist visits. [17]
- If feasible, any dental problems should be attended to before starting bp. [17]
- Smoking cessation, limit alcohol use. [17]
- For patients on bp therapy for more than 3 years, the Canadian Task Force on ONJ suggests the following strategies:
  - Emergency dental work: This should not be delayed; consider stopping bp therapy during healing period. [17]
  - Non-emergency invasive dental work: Consider stopping bp therapy for several months (the American Dental Association recommends 3 months before nonemergency invasive dental procedures and 3 months after during the healing period).
  - The Task Force acknowledges there is no valid evidence that these strategies reduce the risk of osteonecrosis. [17]

- **Atypical fractures**
  - Subtrochanteric and diaphyseal fractures of the femur occurring with little or no trauma. [2]
  - Symptoms of pain and weakness in the groin and thigh area may precede fracturing. [2]
  - The World Health Organization has received over 800 reports of atypical fragility fractures associated with bisphosphonate use. [2]
  - Incidence estimates range from 60 – 100/100,000 patient years. [18,19]
    - Patients on average had been taking a bp for 5 to 6 years. [2]
    - In many cases, patients were also taking hormone therapy or corticosteroid medications. [2]
  - Danish Nation Cohort Analysis published Sept. 2010 [20]:
    - Hazard Ratio for women 1.88 (atypical fracture rate 13/10,000 in untreated vs. 31/10,000 in treated)
    - Hazard Ratio for men 3.98 (6/10,000 in untreated vs. 31/10,000 in treated).
  - Report from the American Society for Bone and Mineral Research task force Sept. 2010 [21]: Causal association between bps and atypical fractures has not been established but physicians and patients should be aware of the potential for this adverse effect. [21]
  - Suggested mechanism: over-suppression of bone remodelling and inability to heal microcracks → increased skeletal fragility. [2]

- May occur at anytime during bp therapy. [22]
- Concurrent glucocorticoid and proton pump inhibitor use may increase risk. [22]

Management:

- In general, discourage bp use in patients at low to moderate risk of fracture unless individual patient factors warrant special consideration. (e.g. some low-risk patients on bisphosphonates due to simply a low BMD may have bisphosphonates stopped opting instead for lifestyle and nutritional interventions such as vitamin D, calcium, weight bearing exercise and addressing tobacco and alcohol use). [2]
- Inform patients with valid indication for bps that the risk of osteoporotic fracture is much higher than risk of atypical fracture. [2]
- In bp monitoring, ask about any unusual bone pain but don't alarm.
- Avoid long-term concurrent use of two antiresorptives. [2]
- Drug holidays are controversial [23,24] – would not be appropriate for high risk patients and discontinuation rather than a holiday might be the better option for low risk patients [25,26].

Renal Dysfunction

- Special considerations are required for patients with renal dysfunction given the potential for IV bisphosphonates to worsen or cause renal dysfunction (e.g. zoledronic acid). [2,9] It is not known if this also occurs with oral bisphosphonates.[2] In patients with renal related bone disease, the risk versus benefit of treating with bisphosphonates is unknown. [2,27,28].
- Manufacturer monographs state that risedronate should not be used if CrCl < 30 ml/min[29]; alendronate [8] and zolendronate (for osteoporosis)[30] if CrCl < 35 ml/min.
- No data on the safety or benefit of reducing dose or increasing the dosing interval in patients with decreased renal function. [24]

Hypocalcemia

- Rare occurrence in otherwise healthy patients.
- Risk factors: hypoparathyroidism, vitamin D or calcium deficiency. [9]

Management:

- Vitamin D and calcium levels should be in the normal range before starting bp especially with IV zoledronic acid. [2,9]
- Calcium and vitamin D supplements during bp therapy as required. [2,3]

Atrial Fibrillation (AF)

- Association between bps and AF has not been confirmed. [29]
- Zoledronic acid increased the risk of severe AF, 1.3 vs. 0.5% over placebo in HORIZON [30]; alendronate increased risk of severe AF, 1.12 vs. 0.8 % in a recent Danish cohort study [31].
- Some observational data for other bps also suggests increased risk of AF, however due to limitations of such trials, it is not yet possible to confirm a true causal association.[2]
- A systematic review and meta-analysis of four randomized controlled trials found a small but statistically significant association between serious AF and bp use – RR 1.5. [32]
- No pharmacological mechanism for this effect has been identified. No dose /duration effect has been demonstrated.[3]
- Bps are used in population group at higher risk of AF.[3]
- FDA recommendation – Do not alter prescribing patterns of bps based on concern for AF. Patients currently on bps should continue therapy. [29]

Other

- **Ocular Adverse Effects**
  - Relatively rare reports of eye inflammation, eye pain, and photophobia associated with both iv and oral bps. [2,3]

Management
- Discontinue bp and refer to ophthalmologist. Rechallenge is not recommended. [2]

- **Skin reactions**
  - Incidence of hives, pruritis similar to antibiotics, anticonvulsants, [2]
  - Serious reactions (e.g. Stevens Johnson Syndrome, Toxic Epidermal Necrolysis Syndrome) very rare. [2]

Generic vs. Brand Name Bisphosphonates

- Anecdotal reports of reduced BMD and increased adverse effects when patients are switched from brand name bps to generic products. [26,33]
- Bps have very poor bioavilability (< 1 %). In theory, small differences in dissolution between different brands could make a significant difference in the amount of drug available to the patient. [33]
- Health Canada data indicate that brand name bps and corresponding generic products are bioequivalent.
- Chart review of 301 women switched from brand name to generic alendronate: significant increase in incidence of adverse effects, primarily GI effects; 47 women discontinued the drug because of adverse effects; 23 women discontinued because of decreased BMD. [34]
- Cohort study of almost 33,000 patients from a Quebec medical database, patients started on generic alendronate were twice as likely to stop the drug as those started on the brand name alendronate. [31]
- However, more robust evidence is needed to support superior therapeutic effect of brand name bps.
- A follow-up BMD after one year is useful to ensure that BMD is not still declining. Non-response may be addressed by switching to an alternate bp and/or addressing adherence and administration/drug interaction issues.

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References:

1. Tosteson A, Grove M, Hammond C. Early discontinuation of treatment for osteoporosis. Am J Med. 2003;115:209 –216.
2. Abrahamsen B. Adverse effects of bisphosphonates. Calcif Tissue Int (2010) 86:421–435.
3. Kennel K, Drake M. Adverse effects of bisphosphonates: implications for osteoporosis management. Mayo Clin Proc 2009;84:632-638.
4. Wysoswski D. Reports of esophageal cancer with oral bisphosphonate use [letter). N Eng J Med 2009;360:89-90.
5. Wysoswski D. Oral bisphosphonates and oesophageal cancer. BMJ 2010; 341:c4506.
6. Cardwell C, Abnet C, Cantwell M et al. Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer. JAMA 2010; 304: 657-663.
7. Green J, Cznner G, Reeves G et al. Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort . *BMJ*. 2010; 341:c4444.
8. e-CPS. Fosamax monograph.
9. Rosen H. Bisphosphonates in the management of osteoporosis in postmenopausal women. UpToDate online. www.uptodate.com. Accessed Aug 2010.
10. Yang Y, Lewis J, Epstein S et al. Long-term Proton Pump Inhibitor Therapy and Risk of Hip Fracture. *JAMA.* 2006;296:2947-2953.

11. Black D, Delmas P, Eastell R et al. HORIZON Pivotal Fracture Trial. One yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809-1822.
12. Bock O, Boerst H, Thomasius F et al. Common musculoskeletal adverse effects of oral treatment with once weekly alendronate and risedronate in patients with osteoporosis and ways for their prevention. J Musculoskelet Neuronal Interact 2007;7:144–148.
13. Delmas P, Benhamou C, Man Z, et al. Monthly dosing of 75 mg risedronate on 2 consecutive days a month: efficacy and safety results. Osteoporos Int. 2008;19:1039-1045.
14. Information for Healthcare Professionals: Bisphosphonates (marketed as Actonel, Actonel+Ca, Aredia, Boniva, Didronel, Fosamax, Fosamax+D, Reclast, Skelid, and Zometa) U.S Food and Drug Administration website. Available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124165.htm . Accessed Sept. 2010.
15. Khosla S, Burr D, Cauley J, et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2007;10:1479-91.
16. Lo J, O'Ryan F, Gordon N, et al. Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. J Oral Maxillofac Surg 2010: 68:243–253.
17. Khan A, Sándor G, Dore E, et al. Canadian consensus practice guidelines for bisphosphonate associated osteonecrosis of the jaw. J Rheumatol. 2008;35:1391-7.
18. Abrahamsen B, Eiken P, Eastell R (2009) Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study. J Bone Miner Res 2009;24:1095-1102.
19. Neviaser AS, Lane JM, Lenart BA, Edobor-Osula F, et al. Low-energy femoral shaft fractures associated with alendronate use. J Orthop Trauma 2008:22:346–350.
20. Abrahamsen B, Eiken P, Eastell R. Cumulative alendronate dose and the long-term absolute risk of subtrochanteric and diaphyseal femur fractures: a register-based national cohort analysis. Clin Endocrinol Metab. 2010 Sep 15. [Epub ahead of print]
21. Shane E, Burr D, Ebeling P et al. Atypical subtrochanteric and diaphyseal femoral fractures: Report of a task force of the American Society for Bone and Mineral Research, J Bone miner Res online. Available at http://onlinelibrary.wiley.com/doi/10.1002/jbmr.253/abstract. Accessed September 2010.
22. Giusti A, Hamdy N, Papapoulos S. Atypical fractures of the femur and bisphosphonate therapy: a systematic review of case/case series studies. Bone 2010;47:169–180.
23. Nelson B. Watts N, Dima L .Long-term use of bisphosphonates in osteoporosis. J Clin Endocrinol Metab 2010; 95: 1555–1565.
24. Schmidt G, Kathleen E. Horner K, McDanel D et al. Risks and benefits of long-term bisphosphonate therapy. Am J Health-Syst Pharm. 2010; 67:994-1001.
25. Rx Files Osteoporosis Treatment Comparison Chart. Available at www.rxfiles.ca.
26. Teleconference with Dr. Olszynski. August 31st, 2010.
27. Gordon PL, Frassetto LA. Management of osteoporosis in CKD Stages 3 to 5. Am J. Kidney Dis. 2010 May;55(5):941-56.
28. Miller PD. Fragility fractures in chronic kidney disease: A clarification of views (December 2009). Cleve Clin J Med. 2010;77(2):75.
29. e-CPS. Actonel monograph.
30. e-CPS. Aclasta monograph.
31. US Food and Drug Administration. Update of Safety Review Follow-up to the October 1, 2007 Early Communication about the Ongoing Safety Review of Bisphosphonates. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm136201.htm . Accessed Sept. 2010.
32. Black D, Delmas P, Eastell R et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809-22.
33. Abrahamsen B, Eiken K, Brixen P. Atrial fibrillation in fracture patients treated with oral bisphosphonates. J Int Med 2009;265:581-92.
34. Bhuriya R, Singh M, Molnar J, Arora R, et al. Bisphosphonate use in women and the risk of atrial fibrillation: A systematic review and meta-analysis. Int J Cardiol 2010;42(3):213-7.
35. Grima1 D, Papaioannou A, Airia1 P et al. Adverse events, bone mineral density and discontinuation associated with generic alendronate among postmenopausal women previously tolerant of brand alendronate: a retrospective cohort study. BMC Musculoskeletal Disorders 2010, 11:68.
36. Sheehy O, Kindundu C, Barbeau M et al. Differences in persistence among bisphosphonate medications. Osteoporos Int (2009) 20:1369–13.